# EVALUATION OF PULMONARY MANIFESTATIONS IN HEMATOLOGICAL MALIGNANCIES

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# BONAFIDE CERTIFICATE

Certified that this dissertation is the bonafide work of **Dr.G.RAVIKUMAR** on "**EVALUATION OF PULMONARY MANIFESTATIONS IN HEMATOLOGICAL MALIGNANCIES"** during his **MD (TUBERCULOSIS AND RESPIRATORY MEDICINE)** course from May 2010 to April 2013 at the INSTITUTE OF THORACIC MEDICINE AND RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL-MADRAS MEDICAL COLLEGE, CHENNAI.

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## DECLARATION BY THE SCHOLAR

I hereby declare that the dissertation entitled **"EVALUATION OF PULMONARY MANIFESTATIONS IN HEMATOLOGICAL MALIGNANCIES"** submitted for the degree of Doctor of Medicine in M.D, degree examination Branch XVII TUBERCULOSIS & RESPITORY MEDICINE is my original work and the dissertation has not formed the basis for the award of any degree, diploma, associate ship, fellowship or similar other titles. It had not been submitted to any other university or institution for the award of any degree or diploma.

Place: Chennai Signature of the scholar

Date: Name: **Dr.G.RAVI KUMAR**

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# CONTENTS

# EVALUATION OF PULMONARY MANIFESTATIONS IN HEMATOLOGICAL MALIGNANCIES

**Background:** Leukemias and lymphomas are a diverse group of disorders in which various pulmonary manifestations are noted. These pulmonary manifestations are dependent upon multiple factors, including the type of leukemia, the nature and time course of treatment, and presence or absence of significant neutropenia and thrombocytopenia. Many of the pulmonary abnormalities are not due to the leukemia itself, but are caused by the patient's immunocompromised status, medications, or a complicating medical illness. Not many studies are available regarding pulmonary manifestations in hematological malignancies. Hence this study was done to analyze the various pulmonary manifestations in these disorders.

**Aim**: To evaluate the pulmonary manifestations of patients with hematological malignancies in a tertiary care Institution

**Method:** Patients diagnosed with hematological malignancies having respiratory manifestations or with chest radiological abnormalities were subjected to various diagnostic tests including CBC, RFT, RBS, LFT, sputum AFB, sputum gram stain, sputum nontuberculous culture, sputum fungal smear& culture, sputum cytology for malignant cells, chest X-ray, CT/HRCT chest, pleural fluid analysis.

**Results**: we included 124 patients (male/female: 42/82) with hematological malignancies (51 Acute Myeloid leukemia, 8 Chronic Myeloid leukemia, 47 Acute lymphoblastic leukemia, 17 Chronic lymphoid leukemia and one Hodgkin lymphoma) who presented with respiratory symptoms and signs during examination. 47% of the patients

had an absolute neutrophil count lower than 1000 cells/µl. out of 124 patients, 60 patients had no parenchymal infiltrates, 6 patients had pleural effusion, 58 patients had parenchymal infiltrates (31 focal/27 diffuse) were identified. An etiological diagnosis was obtained in 109 (88%) of the 124 patients. 60 (48%) patients had Upper respiratory tract infection and acute bronchitis, 28 (22.58%) had bacterial pneumonia, 14(11%) patients had fungal pneumonia, 6 (5%) patients had exudative pleural effusion and one patient was infected with mycobacterium tuberculosis. Bacterial pneumonia predominantly presented as focal infiltrates and fungal pneumonia as diffuse infiltrates. The sputum culture reports were positive more for bacterial organisms followed by fungal organisms. Among them Pseudomonas aeroginosa was the predominant organism, followed by Klebsiella pneumonia and Aspergillus fumigates.

**CONCLUSION:** Pulmonary infections are common cause for increased morbidity and mortality in patients with hematological malignancies. Upper respiratory tract infection and acute bronchitis are the most common associated respiratory diagnosis in patients with hematological malignancies. Neutropenia is the major factor in determining the development of pulmonary infections. Bacterial pneumonia predominantly present as focal infiltrates and fungal pneumonia as diffuse infiltrates. Pulmonary infections are predominantly caused by gram-negative bacteria (Pseudomonas aeroginosa & Klebsiella pneumonia) followed by fungal (Aspergillus fumigates) organisms.

**KEY WORDS:** hematological malignancies, neutropenia, parenchymal infiltrate, pulmonary infection.

# INTRODUCTION

Leukemias and lymphomas are a diverse group of disorders.

Myeloid neoplasms are heterogeneous group of disease which has an origin in a progenitor cell that normally gives rise to terminally differentiated cells of myeloid series (erythrocytes, granulocytes, monocytes and platelets). Three categories of myeloid neoplasia are recognized, they are:

1. Acute myelogenous leukemias, in which immature progenitor cells accumulate in the bone marrow
2. Myelodysplastic syndrome associated with ineffective hematopoiesis and leads to peripheral blood cytopenias
3. Chronic myeloproliferative disorders in which increased production of one or more terminal differentiated myeloid elements usually leads to an elevation of peripheral counts.

Lymphoid neoplasms are a diverse group of entities, in which the neoplastic cells closely resembles that of a particular stage of normal lymphocyte differentiation. Lymphomas can be divided into Hodgkin lymphoma and the non-Hodgkin lymphoma (NHL).

Acute lymphoblastic leukemia/lymphoma (ALL) includes a group of neoplasms composed of immature precursor B (pre-B) or T (pre-T) lymphocytes. Chronic lymphocytic leukemia (CLL) is the most common variety of leukemia, accounting for 30% cases, which composed of mature B lymphocytes.

Pulmonary complications are common in patients with any of the hematological malignancies. These pulmonary manifestations are dependent upon multiple factors, including the type of leukemia, absence of significant neutropenia and thrombocytopenia and the nature and time course of treatment. Many of the pulmonary abnormalities are not due to the leukemia itself, but are caused by the patient's immunocompromised status, chemotherapy and radiotherapy, or a complicating medical illness.

In leukemia, the true incidence of pulmonary complications is difficult to assess because most articles reported are selected for patients with specific pulmonary complications or particular leukemias. Moreover, the incidence of pulmonary manifestations varies over a wide range, depending upon whether symptoms, sputum analysis, chest radiographs, CT chest, bronchoalveolar lavage or histopathological findings alone are used as the index of disease.

In patients with hematological neoplasms, the most common pulmonary complication is infections with bacterial or opportunistic pathogens. Pleural effusions in hematological malignancies may occur as an isolated finding or associated with parenchymal abnormalities, occur usually in patients with hematological malignancies. The causes for pleural effusions are pleural involvement by neoplasm, infection, lymphatic obstruction, fluid overload and radiation or chemotherapy effects.

Not many studies are available regarding pulmonary manifestations in hematological malignancies. Hence this study was done to analyze the various pulmonary manifestations in these disorders.

# AIM OF THE STUDY

To evaluate the pulmonary manifestations of patients with hematological malignancies in a tertiary care Institution.

# REVIEW OF THE LITERATURE

The primary mode of search for articles was through internet database like ‘pub med’, “Google scholar” and hand search of articles. The general search items were ‘hematological malignancies’, ‘pulmonary complications’, ‘pneumonia’, ‘neutropenia’ and ‘radiological features’. The articles included in this review were those that primarily dealt with pulmonary complications of leukemia, non-invasive diagnostic approach in non-immunocompromised patients with pulmonary infiltrates, those dealt with pleural effusion in hematological malignancies, tuberculosis in leukemia & lymphoma, fungal infections in hematological malignancies, febrile neutropenia and those dealt with pulmonary parenchymal infiltrates in neutropenia with hematological malignancies during chemotherapy. Articles in languages other than English for lack of comprehension were excluded.

Leukemias and lymphomas are a heterogeneous group of neoplasms in which various pulmonary manifestations are noted. These pulmonary manifestations are not only dependent upon the type of leukemia, and also type of treatment, and presence or absence of significant neutropenia and thrombocytopenia. Pulmonary

complications in hematological malignancies are not due to the primary neoplasm itself, but are caused by the patient's immunocompromised status, chemotherapy, or co morbidities like diabetes mellitus, chronic renal failure, etc...

## CLASSIFICATION OF ACUTE LEUKEMIA (AL) & MYELODYSPLASTIC SYNDROME (MDS)

- Acute lymphoid leukemia
- Precursor-B cell lymphoblastic leukemia/lymphoma
- Precursor-T cell lymphoblastic leukemia/lymphoma
- Burkitt lymphoma/ leukemia
- MDS
- Acute myeloid leukemia (AML)
- Acute leukemia (AL) of ambiguous lineage

## WORLD HEALTH ORGANISATION (WHO) CLASSIFICATION OF MALIGNANT LYMPHOMAS

### B-CELL NEOPLASMS

PRECURSOR B-CELL NEOPLASM

- Precursor-B cell lymphoblastic leukemia/lymphoma

MATURE B-CELL NEOPLASM

- Follicular lymphoma
- Chronic lymphocytic leukemia/ small lymphocytic leukemia
- Lymphoplasmocytic lymphoma
- Mantle cell lymphoma
- Nodal marginal zone B-cell lymphoma
- Splenic marginal zone B-cell lymphoma
- Extra nodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue
- Diffuse large B-cell lymphoma
- Mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma

- Primary effusion lymphoma
- Burkitt lymphoma

## T-CELL AND NK-CELL NEOPLASM

### PRECURSOR T-CELL NEOPLASM

- Precursor-B cell lymphoblastic leukemia/lymphoma

### MATURE T-CELL AND NK-CELL LYMPHOMA

- Peripheral T-cell lymphoma, unspecified
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma
- Adult T-cell leukemia/ lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniclitis-like T-cell lymphoma
- Enteropathy- type T-cell lymphoma
- Mycosis fungoides/sezary syndrome
- Extra nodal NK/T-cell lymphoma, nasal type
- Aggressive NK-cell leukemia

**HODGKIN LYMPHOMAS**

CLASSICAL

- Mixed cellularity
- Lymphocyte-rich
- Nodular sclerosis
- Lymphocyte-depleted

NODULAR LYMPHOCYTE-PREDOMINANT

## ACUTE MYELOID LEUKEMIA (AML)

Acute myeloid leukemia (AML) refers to a group of myeloid leukemias that have clinical similarities and distinct morphologic, cytogenic, immunophenotypic, and molecular features.

AML is more common in adults, but may occur at any age, with increased frequency as age advances. Clinical features of Acute myeloid leukemia are similar at all age and are due to the replacement or suppression of normal marrow components, by malignant blasts, usually resulting in impaired hematopoiesis manifested by cytopenias.

In Acute myeloid leukemia, the malignant cells are a blast that most often shows myeloid or monocytic differentiation. The myeloid blast cell can be identified by the presence of Auer rods or by Sudan black, Chloroacetate esterase, Myeloperoxidase (MPO), or Non specific esterase positivity on cytochemical stains. In addition to these findings, flow cytometry is used to classify acute myeloid leukemia based on the presence of lymphoid and myeloid antigens.

## ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Acute lymphoblastic leukemia (ALL) is a malignant disease that originates from a single B- or T- lymphocyte progenitor. Proliferation and infiltration of malignant cells in the bone marrow result in suppression of hematopoiesis and, leads to fall in counts of granulocyte, erythrocyte and platelets.

Acute lymphoblastic leukemia (ALL) is predominantly occurs in children and young adults. The etiology of Acute lymphoblastic leukemia in adults most of the cases is uncertain. ALL is unlikely in middle-aged adults but increases in incidence in the elderly.

Acute lymphoblastic leukemia is a hematological malignancy that is rapidly fatal if untreated.

Environmental exposures, smoking, and exposure to agricultural chemicals might increase the risk of developing ALL in an adult.

Blast cells in Acute lymphoblastic leukemia is negative for Myeloperoxidase (MPO), instead of which positive for Periodic acid shiff (PAS).

## CHRONIC MYELOID LEUKEMIA (CML)

Chronic myeloid leukemia is the most common of the myeloproliferative disorders.

It can occur at any age, although it is unlikely in children. The average age at diagnosis is 50 to 60 years. CML is more common in males when compare to females.

Chronic myeloid leukemia is defined by the presence of the Philadelphia chromosome or molecular genetics evidence of the BCR/ABL fusion product. Chronic myeloid leukemia is primarily a proliferation and accumulation of granulocytic cells.

The peripheral blood features are those of a increase in leukocyte count with granulocytes at all stage of maturation, increased number of myelocytes and metamyelocytes, Eosinophilia, Absolute monocytosis, Basophilia, and elevated level of platelets. The bone marrow is characterized by marked hypercellularity with a cellularity approaching 100%.

## CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Chronic lymphocytic leukemia is one of the most common type of leukemia in western countries. This is an uncommon neoplasm in Asia. CLL is more common in men than in women. The etiological factors for CLL are unknown in most of cases.

Chronic lymphocytic leukemia is a malignancy of small round CD5+ B-cells.

CLL is the word used to describe the disorder when lymph node involvement is the predominant feature.

Usually, these lymphomas most commonly present in elderly patients with a leukemic phase and generalized lymphadenopathy on physical examination. Bone marrow involvement in CLL is often extensive. CLL is characterized by the proliferation and accumulation of mature-appearing lymphocytes in the marrow, blood, lymph nodes, and spleen.

## HODGKIN LYMPHOMA (HL)

Hodgkin lymphoma, in its simplest pathology defined as a neoplasm of Reed-Sternberg cells and RS cell variants that are usually associated with inflammatory response that often predominate the morphologic picture.

Hodgkin lymphoma clinically presents as solitary or generalized lymphadenopathy. Hodgkin lymphoma most commonly occurs in males than females. A bimodal distribution of age at diagnosis has been observed in Hodgkin lymphoma, with one peak incidence occurring in patients in their twenties and again in those in their eighties.

Classic Hodgkin lymphoma is a malignant disorder of lymphoid tissue, commonly originated from germinal center B cells. Classic HL accounts for 95% of cases.

Classical variety contains four histologic subtypes and they are nodular sclerosis, mixed cellularity, lymphocyte-rich and lymphocyte-depleted. Four histologic subtypes are distinguished on the basis of morphologic appearance and relative proportion of Reed-Sternberg cells, lymphocytes, and fibrosis.

Nodular lymphocyte-predominant represents the other major category of Hodgkin lymphoma.

## PULMONARY COMPLICATIONS IN PERSONS WITH LEUKEMIAS AND LYMPHOMAS

- Infection
- Involvement of malignant blast cells

    Stasis of malignant cells

    Blast cell lysis

    Hyperleukocytic reaction

- Hemorrhage
- Complication of chemotherapy
- Alveolar proteinosis

# PULMONARY INFECTIONS IN HEMATOLOGICAL MALIGNANCIES

Most common cause for morbidity and mortality in patients with leukemias and lymphomas are infection. Chest is the commonest site of infection in those with hematological neoplasm (1).

In patients with leukemias and lymphomas, pulmonary infiltrates seen on radiological investigations are generally considered to be of infective etiology. In presence of pulmonary infiltrates with fever, such patients are treated on Empirical antibiotics along with antifungal agents. In most of patients these pulmonary infiltrates persists in spite of empirical treatment, and the cause remains obscure.

Specific diagnosis and institution of specific treatment in this group of patients promptly would be very critical to decrease the mortality and morbidity in patients with hematological malignancies (2).

Patients with hematological malignancies, especially acute leukemia have increased risk of severe infection with gram-negative bacterial organisms as a result of quantitative or qualitative neutropenia.

In Chronic lymphocytic leukemia and multiple myeloma, patients are susceptible to bacterial infections from Staphylococci and streptococci.

In contrast to that, patients from lymphoma have defect in their cellular immune system that results in increased risk of viral and fungal infections. In patients with lymphoma therapeutic interventions such as corticosteroids, cytotoxic chemotherapy and radiation also cause defect in the host defense (3).

A Rano et al in his study recommended using non-invasive investigations as a initial step in the evaluation and management of pulmonary infiltrates in patients with immunocompromised status, especially those with hematological malignancies. These investigations include blood and sputum culture. In 44% of the cases use of non-invasive technique provides the diagnosis and constitutes a good alternative for a bronchoscopic investigation (4).

S Ewig et al quoted in his article as principle reason for pulmonary abnormalities and hospitalization in those with hematological malignancies was infection (5).

Gerald P Bodey et al in his study concluded that in 34% of the episode of infections were caused by pneumonia (6). Sarah P Georgiadou et al in their study found that pulmonary infections were more common in patients with acute leukemias (36% AML & 12% ALL) (7).

## SPECTRUM OF MICROBIOLOGICAL PATHOGENS IN HEMATOLOGICAL MALIGNANCIES.

Over the last four decades there has been a marked change in the pathogens producing infections in immunocompromised patients, especially those with hematological malignancies.

In the early 1950s and 1960s among the bacterial organisms Staphylococcus aureus was the most common isolate in persons with hematological malignancies (8). With the increase in use of beta lactamase resistant antistaphylococcal pencillins in treatment, leads to emergence of gram-negative bacilli as the common cause for infection, especially with pseudomonas aeroginosa, Klebsiella pneumoniae and Escherichia coli.

Since the 1980s, several studies have demonstrated a shift in the etiology of bacterial infections from a predominance of gram-negative pathogens to gram-positive cocci (3).

Fungal infections are more common, especially in patients with prolonged & severe neutropenia and who receive prolonged courses of antibiotics (9). The most frequent isolates among fungal pathogens are Aspergillus species, Candida species and C.neoformans.

Jagarlamudi R et al in his study says that bacterial pneumonias in patients with hematological malignancies were commonly caused by gram-positive pathogens (52.8%) than gram-negative pathogens (42.8%) (10).

S Shawgi et al founded that bacterial pneumonias were most commonly caused by gram-negative organisms in his study (2).

Baladuci and associates documented that, 193 patients with hematological malignancies were affected by infection, among which 50% of infection were occurred in respiratory tract. In these group of patients Pseudomonas aeroginosa, Escherichia coli, Klebsiella pneumoniae, and Staphylococcus aureus were the frequent cause of infection.. Other causes like Fungi (Candida, Aspergillus) and Virus are less frequent organisms (11).

A Rano et al in his study says that Staphylococcus aureus, and gram-negative bacilli mainly Pseudomonas aeroginosa were the most

frequent cause for infections in respiratory tract. Fungal organisms, especially Aspergillus species represents the second most frequent infectious cause of pulmonary infiltrates (4). Although evidence of tissue invasion by fungal organism has classically been required to confirm the diagnosis of fungal infections, the presence of Aspergillus species in sputum or bronchial lavage culture should be considered indicative of invasive fungal disease until proved otherwise and warrants institution of specific anti fungal therapy (12).

S Ewig et al documented that pneumonia was most frequently caused by bacterial organisms followed by fungal organisms. In bacterial pneumonia Pseudomonas aeroginosa was the most common pathogen, in fungal pneumonia Candida species was the most common pathogen (5).

Jain P et al in his study viewed 104 immunocompromised patients with pulmonary infiltrates, among them 49% of patients had bacterial infection, 26% of patients had viral infection, 21% of patients had fungal infection and 4% infections with P.jirovecii. The most common organism identified with those bacterial pneumonias was Pseudomonas aeroginosa and Staphylococcus aureus followed by Escherichia coli. Aspergillus species is the common cause for fungal infection in this study (13).

Santiago Ewig et al in his study says that gram-positive organisms accounted for 52% of respiratory tract infection, gram negative pathogens for 36% of respiratory tract infection, and fungal organisms for 8% of respiratory tract infection (14).

## NEUTROPENIA

Neutropenia is defined as an absolute neutrophil count (polymorphonuclear cells plus band forms) of 1000/µl or less.

Neutropenia, resulting from the effect of cytotoxic chemotherapy is the most common risk factor for severe bacterial and fungal infections in hematological malignancies. The degree of Neutropenia either as a consequence of hematological malignancy or chemotherapy is directly related to the incidence of serious bacterial and fungal pneumonias.

There is a significant increase in the incidence of serious bacterial & fungal infection once Absolute neutrophil count falls below 500cells/µl. patients with Absolute neutrophil count below 100cells/µl are at the greatest risk of fulminant lung infection.

Both quantitative and qualitative defects in neutrophil function have been demonstrated in hematological malignancies. Qualitative defects include defects in chemotaxis, phagocytosis, and absence of respiratory burst that accompanies phagocytosis. In addition to that chemotherapeutic agents including corticosteroids also decrease neutrophil function like phagocytosis and neutrophil migration (3).

Granulocytopenia is a major determining factor for occurrence of infections especially involving lungs. A direct correlation has been demonstrated between the fall in Absolute neutrophil count and the increased incidence of infection. With Absolute neutrophil count below 1000 cells/µl, there is a significant increase in incidence of respiratory infection and counts below 100cells/µl gram negative bacteremia and other fungal infections (15).

Greson and others found in their study that, neutropenia to be the major risk factor in occurrence of invasive pulmonary mycosis (16). Up to 60% 0f patients, with a neutrophil count of less than 1000 cells/µl develop lung infiltrates at sometime during the course of the disease, most commonly due to infectious etiology (17).

In patients with neutropenia commonest site of infection is Respiratory tract (18).

## RADIOLOGICAL FINDINGS IN HEMTOLOGICAL MALIGNANCIES

Maj Michael F et al reviewed the inpatient records of 139 adult patients with leukemia and lymphoma to analyze the occurrence of bacterial and opportunistic infections and radiological abnormalities in such patients.

Fifty two (37%) of the 139 patients had no parenchymal infiltrates throughout their course in hospitalization. Twenty three patients of the 139 had only non parenchymal abnormalities like pleural effusion, mediastinal widening and hilar adenopathy.

He also observed in his study that during the course of chemotherapy parenchymal abnormalities occurred on 81 separate occasions in 70 patients. The roentgenographic pattern was that of local disease in 31 instances (38%) and that of diffuse disease in 50 instances (62%).

A cause for the disease process could be established in 90% (28/31) of local disease and in 80% (40/50) of diffuse disease. Of the 28 episodes of local disease, in which infectious cause accounted for 82% (23/28), however an opportunistic organisms responsible only for 11% (3/28). In patients with diffuse disease in whom a cause could be

determined, infectious cause accounted for 35% (14/40). Ninety three percent (13/14) of diffuse disease caused by opportunistic organisms.

This study documented that bacterial and opportunistic infections are primary complications of acute leukemia. Infiltrates with local distribution are frequently bacterial infections and for diffuse distribution opportunistic organisms are frequent etiology (19).

M Von Eiff et al in his study documented that for both Aspergillus and Candida infections, bilateral diffuse pulmonary infiltrates is the commonest presentation in patients with acute leukemias (20).

## BACTERIAL PNEUMONIA

Occurrences of Bacterial infections differ in frequency depending on underlying host immune defects.

Among which gram-negative bacteria like Pseudomonas aeroginosa and Klebsiella pneumoniae predominate in patients with hematological malignancy in which neutrophils are quantitatively or qualitatively impaired and chemotherapy induced neutropenia occur.

In patients with Multiple Myeloma or Chronic Lymphocytic Leukemia in whom abnormalities in the quantity or function of immunoglobulin are common and opsonisation impaired, encapsulated bacteria like Streptococcus pneumoniae and Hemophilus influenza are most common etiological agent for bacterial pneumonia.

Importantly in those with neutropenia, Staphylococcus aureus and Streptococcus viridians emerged as a most common pathogen for pneumonia as a result of prophylactic administration of antibiotics which act against gram negative bacteria.

Incidence of Staphylococcus aureus infection is more common in elder age group than in younger adults, and in those with risk factors for infection such as diabetes mellitus and alcohol intake.

The term gram negative bacillary pneumonia refers to infections caused by members of two groups, the Enterobacteriaceae and pseudomonaceae.

At least 40% to 45% of Hospital Acquired Pneumonia in patients with leukemias is caused by Enterobacteriaceae such as Escherichia, Klebsiella, Enterobacter, Proteus, Serratia, Salmonella and citrobacter.

The Enterobacteriaceae normally colonize the digestive tract and pneumonia usually results from aspiration of oropharyngeal flora. Pneumonia caused by Enterobacteriaceae group of organisms is uncommon in healthy, non hospitalized individuals. The prevalence of oropharyngeal colonization by gram negative bacilli especially Enterobacteriaceae group is greatly increased by serious co-morbidities, immunocompromised state, hospitalization, risk of aspiration and antimicrobial use. Mortality due to Enterobacteriaceae pneumonia is 25% to 50%. Presence of neutropenia, bacteremia and old age points to a poor prognosis in those patients infected with gram-negative bacilli.

Pseudomonas aeroginosa is a gram negative bacillus that is ubiquitous in environment and one of the most common opportunistic pathogen in humans.

Among the anatomic location of Pseudomonas aeroginosa infection, the lung is the most common one and associated with highest mortality rate. The characteristic feature of pneumonia due to Pseudomonas aeroginosa is its occurrence in immunocompromised patients with hemorrhagic and necrotizing lung pathology. Patients in whom clinical manifestations of pneumonia exits along with a new pulmonary infiltrates, isolation of Pseudomonas aeroginosa from respiratory secretions, is often considered to be circumstantial evidence that Pseudomonas aeroginosa is the cause for pneumonia and it becomes the basis for initiation of anti pseudomonal antibiotic therapy.

## FUNGAL PNEUMONIA

Among fungal infections, Aspergillus and Candida species are one of the most common pathogens, which constitute a major increasing cause for infection during the chemotherapy treatment of patients with hematological malignancies.

Diagnosis of invasive fungal infections during antemortam period is difficult one. The initial clinical and radiographic presentation of invasive fungal pneumonia is indistinguishable from those of other infectious pneumonia. In patients with severe neutropenia, clinical and radiological findings in the lungs are often absent. In patients with hematological malignancies thrombocytopenia or blood coagulation disorders are frequent, so biopsy is often contraindicated. High resolution computed tomography has been associated in the early diagnosis and management of opportunistic fungal pneumonia.

Livio Pagno et al in his study documented that the primary site of fungal infection are lungs (85%) in patients with leukemias and lymphomas. In 77% of patients with pulmonary filamentous fungal infection, chest x ray is a valuable diagnostic method, while CT scan being the most superior in detecting this in 95% of patients. Majority of infection with fungal pathogens occur in patients with hematological

malignancies, particularly Acute Myeloid Leukemia (AML). Aspergillus was the agent of filamentous fungal infection most frequently isolated in 76% 0f patients (296 cases). Aspergillus fumigates was the main agent among them (21). In patients with hematological malignancies Strong clinical or radiological evidence of fungal infection should be treated with full course of anti fungal therapy.

Candida pneumonia was first described in 1771 by Rosen Von Rosenstein. The most common predisposing factor proposed for Candida pneumonia is immunosuppression and neutropenia, mostly in malignant disease. Prolonged broad spectrum antibiotic therapy and prolonged corticosteroid therapy are also common predisposing factors for Candida infection. The positive sputum culture although not diagnostic for Candida, will arise a suspicion of Candida pneumonia.

Zab Mohsenifar and others in their study documented that the radiological findings of Candida pneumonia in patients with hematological malignancies. He found that 80% (16/20) of patients presented with diffuse infiltrates and 20% (4/20) 0f patients presented with focal infiltrates and concluded that diffuse infiltrates are the most common radiological findings in Candida pneumonia (22).

Aspergillus is a saprophytic organism, which is ubiquitous in the environment. Respiratory tract is the commonest site of aspergillus infection. Depending essentially on the host's immunological status, Aspergillus species can give rise to various clinical manifestations. Invasion of pulmonary parenchyma by aspergillus species, especially in those patients with prolonged neutropenia leads to invasive pulmonary aspergillosis.

## TUBERCULOSIS IN HEMATOLOGICAL MALIGNANCIES

Tuberculosis infections are serious and life threatening complication in patients with hematological malignancies. Chances of reactivation of latent tuberculosis are more during chemotherapy with cytotoxic drugs and steroid for prolonged period (23).

Incidence of Tuberculosis in patients with hematological malignancies range between 2.1%to 2.6% (24). Clinically evident tuberculosis can antedate hematological malignancy, or both may present simultaneously or tuberculosis infection may develop after the treatment of the malignant disorders with chemotherapy.

Tuberculosis occurs predominantly in males than females and in patients with Chronic myeloproliferative disorders, Acute myeloid leukemia and Myelodysplasia. The more intensive cytotoxic chemotherapy that is repeated courses of intravenous chemotherapy rather than oral chemotherapeutic agents, given for the primary hematological malignancies, leads to the earlier development of tuberculosis and the infection would be disseminated more likely.

# PLEURAL EFFUSION IN HEMATOLOGICAL MALIGNANCIES

Pleural effusion, either as isolated entity or associated with parenchymal lung infiltration, occur regularly in patients with hematological malignancies.

Michael G. Alexandrakis et al, in his review article about " pleural effusion in hematological malignancies" says that, the amount of pleural fluid accumulated in lymphomas may vary, ranging from little or no respiratory symptoms, and blunting of the costophrenic angle on chest radiography, to severe respiratory distress on clinical examination with opacification of a whole hemi thorax. The pleural fluid may appear serous or serosanguineous. In lymphomas, Pleural effusions are usually exudates.

He described about possible mechanisms for the formation of pleural effusions in patients with hematological malignancies include the following

1. Pleural infiltration by the neoplasm with shedding of malignant cells into the pleural space
2. Lymphomatous infiltration of the pulmonary and mediastinal lymph nodes by malignant cells leads to Lymphatic obstruction
3. Obstruction of thoracic duct

Pleural involvement in Patients with Chronic Lymphocytic Leukemia (CLL), usually have a long standing diagnosis of CLL before the pleural effusion develops (25).

Jon Bais, MD et al discussed like that, most of the pleural effusions in which a thoracentesis was undertaken were moderate to large in size (87%) and were associated with parenchymal abnormalities (69%). Both bilateral effusions (62%) and unilateral effusions (38%) were subjected to thoracentesis. Exudates were documented in 83% of patients and 10% were tansudate and 7% were unclassified (26).

# MATERIALS AND METHODS

## STUDY DESIGN

This is Prospective (Observational) study designed to find the pulmonary manifestations of patients with hematological malignancies in a tertiary care Institution.

## STUDY CENTER

Department of thoracic medicine, Rajiv Gandhi Government general Hospital & Madras Medical College, Chennai-3.

Department of Hematology, Rajiv Gandhi Government general Hospital & Madras Medical College, Chennai-3.

## STUDY DURATION

February 2012 to October 2012

## STUDY POPULATION

Patients of >12 years of age with diagnosis of hematological malignancies, with respiratory symptoms or signs during examination or with radiological abnormalities were included in this study.

Proforma was designed and ethical committee clearance was obtained. A written informed consent was obtained from all patients included in this study after explaining in detail the nature and purpose of the study.

## INCLUSION CRITERIA

1. age >12 years
2. Any patient diagnosed with hematological malignancies presenting with respiratory symptoms /having respiratory signs during examination / with radiological abnormalities

## EXCLUSION CRITERIA

1. Patients those who are not willing to give consent
2. Patients too ill for a detailed work up were excluded

## STUDY PROCEDURE

124 inpatients in the Hematology & Thoracic medicine department with respiratory manifestations who satisfied the above inclusion & exclusion criteria were enrolled in this study. After obtaining informed consent from them they were examined clinically after a detailed history.

These patients were subjected to various diagnostic tests including

- Complete blood count
- Random blood sugar
- Renal function test
- Liver function test
- HIV testing
- Sputum for Acid Fast Bacilli
- Sputum for Gram stain
- Sputum for aerobic bacterial culture
- Sputum for fungal smear &culture
- Sputum for malignant cells
- Chest X ray

Patients with pleural effusion in chest x ray were subjected to diagnostic thoracentesis, and the pleural fluid has been sent for

- Biochemical analysis like sugar, protein and lactate dehydrogenase
- Cell count
- Cytology for malignant cells
- Acid fast stain
- Gram stain & aerobic bacterial culture
- Fungal smear & fungal culture.

In patients with abnormal roentgenographic findings were subjected to CT chest/ high resolution CT chest.

**GRAM STAIN TECHNIQUE**

A new unscratched slide was selected. A loopful of sputum had been transferred to the surface of a clean glass slide with a wooden stick and was smeared over a small area. Then the smear had been allowed to air dry. The air dried film was fixed by passing it briefly through the Bunsen flame two or three times without exposing the dried smear directly to the flame. The slide should not be hot as to be uncomfortable to the touch. Then slide was flooded with crystal violet solution for up

to one minute, and washed briefly with tap water (not over 5 seconds) , again the slide was flooded with Gram's Iodine solution and allowed to act (as a mordant) for about one minute. The slide was washed in running tap water. Excess water had been removed from slide with blotting paper, so that alcohol used for decolorization was not diluted. The slide then flooded with 95% alcohol for 10 seconds and washed again with tap water (smear that are excessively thick may require longer decolorization time. Decolorization procedure is the most sensitive and variable step of grams stain technique, and it requires experience to know just how much to decolorize the slide). The slide was stained with Safranin solution, which acts as a counter stain and allowed to act for 30 seconds. The slide again washed in tap water and dried with bibulous paper. Slide was examined under oil immersion lens.

**BACTERIAL CULTURE**

Fresh sputum collected in a sterile container with screw cap had been sent for examination. Care had been taken that the specimen is sputum and not saliva. Examination of Gram stain, with number of epithelial cells and polymorphonuclear leukocytes had been noted.

Blood agar, Chocolate agar and Mac conkeys agar were the culture medium has been used for aerobic bacterial culture.

## FUNGAL SMEAR & FUNGAL CULTURE

The laboratory diagnosis of fungus infection was made by microscopic examination of sputum, which was usually examined as wet mounts after treatment with 10% potassium hydroxide. Potassium hydroxide digests cells and other tissue materials, and enabling the fungus elements to be seen clearly. First morning sputum was collected for fungal culture, before that procedure patient had been instructed to rinse his mouth, collect sputum resulting from a deep cough and expectorate the sputum immediately into a sputum collection container, without holding sputum in the mouth. The commonest culture media used in this study was Sabouraud's glucose agar. Identification was based on morphology of the fungus and of its colony. Sensitivity of the organisms to antifungal drugs was not done in our study.

## ZIEHL- NEELSON STAINING METHOD

A new unscratched slide was selected. The slide was labeled with the laboratory serial number using a diamond marking pencil. Smear was made from the yellow muco-purulant portion of the sputum sample

using a loop. Smear was spread evenly, about the size of 2cm x 2cm, smear was made neither thick nor too thin. Then slide was allowed to air dry for 15 to 30 minutes. The smear was then fixed by passing it over a flame 3 to 5 times, for 3 to 4 seconds each time. 1% Carbol fuschin, primary stain was poured to cover the entire slide. After which the slide was then gently warmed with the Carbol fuschin on it, until vapors arose. Care has been taken not to let it boil. After boiling Carbol fuschin was left on the slide for five minutes. Then the slide was rinsed under tap water until all the free Carbol fuschin stain was washed away. For decolorizing the primary stain, 25% Sulphuric acid was then poured onto the slide. The slide was left to stand for 2 to 4 minutes. Then it was gently rinsed under tap water, and then slide was tilted to drain off the water.

0.1% Methylene was poured onto the slide, then left on the slide for 30 seconds. The slide was then gently rinsed under tap water and allowed to dry. The slide was then examined under microscope using the 40x lens to select a suitable area then examined using 100 x lenses with a drop of immersion oil (27).

## DIAGNOSTIC THORACENTESIS

Once the site of thoracentesis was identified, the site was marked by exerting pressure using the end of a ballpoint pen with the tip retracted. Then the skin surrounding the proposed site over an area extending at least 4 inch in all directions was cleansed thoroughly with an antiseptic solution. By using a short 25-gauge needle, the skin was anaesthetized by injecting enough lignocaine, around 0.5 ml, to raise a small wheal in skin. The small 25-gauge needle is then replaced by a 1.5 inch long 22-gauge needle. This long needle was inserted to the periosteum of the rib underlying the proposed thoracentesis site, and the needle was moved up and over the rib with frequent injection of small amounts of lignocaine. Once this needle was superior to the rib, then it was slowly advanced toward the pleural space with frequent aspiration, followed by injection of lignocaine 1 to 2 mm. As soon as the pleural fluid was aspirated through this needle into the syringe containing lignocaine; the needle was withdrawn from the pleural space and reattached to 20 ml syringe. The same long 22-gauge needle was reintroduced along the same tract with constant aspiration until pleural fluid was obtained. Once pleural fluid was obtained aspiration was then continued until the syringe was filled. After that, needle was withdrawn,

and the procedure was finished. Aspirated fluid was then sent for Biochemical analysis (protein, glucose and lactate dehydrogenase), cell count, Gram's stain, aerobic bacterial culture, acid fast stain, fungal smear and culture, and cytology for malignant cells.

## DEFINITIONS AND CRITERIAS

### FEVER

Fever was defined as single reading of oral temperature ≥ 101 F recorded or two values >100.4 F recorded at least one hour apart, and it was unrelated to blood product transfusions or chemotherapy drug administration (2).

### NEUTROPENIA

Neutropenia is defined as an absolute neutrophil count (polymorphonuclear cells plus band forms) of 1000/µl or less (3).

### RADIOLOGICAL FINDINGS

**FOCAL**- if there is lobar or segmental involvement

**DIFFUSE**- all other parenchymal abnormalities (28)

## UPPER RESPIRATORY TRACT INFECTION

The International Classification of health problems in primary health care defines “upper respiratory tract infections” as acute inflammation of nasal or pharyngeal mucosa in the absence of other specifically defined respiratory infection. It consist of nasopharyngitis (common cold), pharyngitis, otitis media, sinusitis, laryngitis and acute bronchitis (29).

## ACUTE BRONCHITIS

For the diagnosis of acute bronchitis at least two of the following symptom and sign should be present: increased frequency and severity of cough, new or increased sputum production, fever (temperature ≥38$^{o}$C), and burning substernal chest discomfort with coughing or deep inspiration. Radiologic evidence of pneumonia excluded the diagnosis of acute bronchitis (29).

## PNEUMONIA

Pneumonia is defined as inflammation and consolidation of lung tissue due to an infectious agent and characterized by radiographic infiltrate. Pneumonia can be classified as follows:

Community acquired pneumonia

Nosocomial pneumonia

Ventilator associated pneumonia

Hospital acquired pneumonia

Health care associated pneumonia

## COMMUNITY ACQUIRED PNEUMONIA

Pneumonia that develops outside the hospital is considered Community acquired pneumonia (CAP)

## HOSPITAL ACQUIRED PNEUMONIA (HAP)

Pneumonia that is neither present nor incubating at the time of admission and occurring after 48 hours of admission.

## VENTILATOR ASSOCIATED PNEUMONIA

Complicates Intubation Process

Early onset-occurring VAP in 48-72 hrs

Late onset- occurring VAP after 72 hrs

## HEALTH CARE ASSOCIATED PNEUMONIA

- Patients with pneumonia developing in 2 to 90 days of hospitalization
- Recent exposure to hemodialysis, I.V antibiotics chemotherapy, wound care
- Resident of nursing home
- Person may be residing in a community but he was infected with organism similar to HAP.

## OPPORTUNISTIC INFECTIONS

Those caused by Fungus, Cytomegalovirus, Parasitic disease, or Mycobacterium. (19)

## BACTERIAL PNEUMONIA

- Productive cough
- Lung infiltration on chest radiography
- Fever ≥38.4º c

With one of the following

1. Positive blood or pleural fluid or sputum culture
2. PSB culture showing ≥ $10^3$ CFU/ml

3. Quantitative BAL culture showing $\geq 10^5$ CFU/ml
4. Complete resolution of clinical or radiological signs with a course of antibiotic therapy

**FUNGAL PNEUMONIA**

- Fever resistant to antibiotic therapy for more than 5 days
- Appearance of new pulmonary infiltrates
- Histological demonstration of pulmonary invasive disease or positive cultures in sputum or bronchoscopic specimen (20).

**PULMONARY TUBERCULOSIS**

. Diagnosis by microscopic examination of a sputum smear prepared by ziehl- neelson staining method detecting the acid fast bacilli.

**LIGHT'S CRITERIA**

This is the first step to determine whether the pleural effusion is a transudate or exudate. Light's criteria were used to differentiate exudative pleural effusion from transudative pleural effusion. Exudative

pleural effusion meets at least one of the following criteria, whereas transudative pleural effusions meet none:

- Pleural fluid protein divided by serum protein greater than 0.5
- Pleural fluid LDH divided by serum LDH greater than 0.6
- Pleural fluid LDH greater than two thirds of the upper limit of normal serum LDH

# RESULTS

In this study 124 patients with hematological malignancies were enrolled. All the patients were subjected to microbiological and radiological investigations. Results from those investigations were analyzed statistically, and the results of which were as follows.

## DEMOGRAPHY

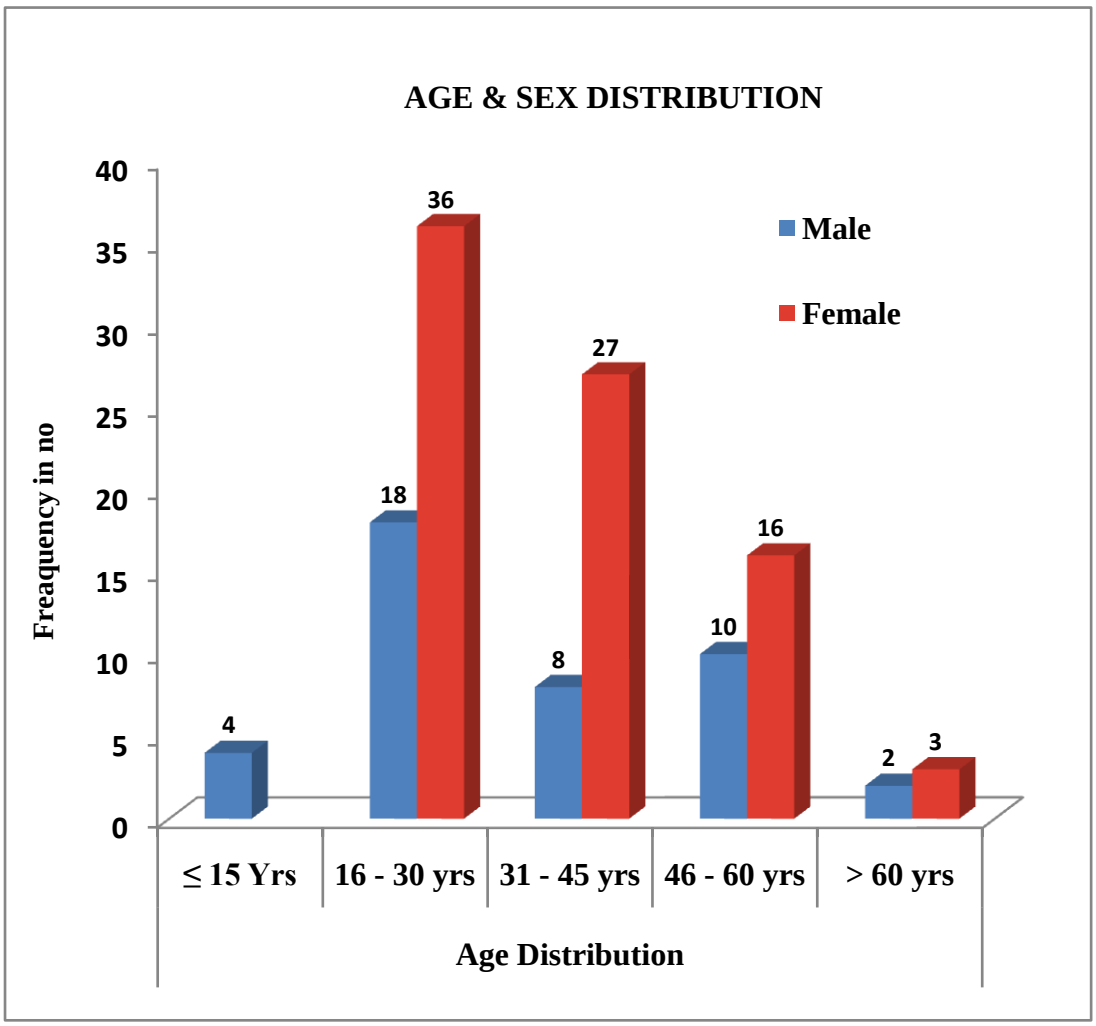
## AGE AND SEX DISTRIBUTION

**TABLE 1:**

| SEX | AGE DISTRIBUTION | | | | | Total |
|---|---|---|---|---|---|---|
| | **≤ 15 Yrs** | **16 - 30 yrs** | **31 - 45 yrs** | **46 - 60 yrs** | **> 60 yrs** | |
| **MALE** | 4 | 18 | 8 | 10 | 2 | 42 |
| **FEMALE** | - | 36 | 27 | 16 | 3 | 82 |
| Total | 4 | 54 | 35 | 26 | 5 | 124 |

The highest incidence of hematological malignancies was noted in the 16-30 years age group. Among all age groups, there was a female preponderance.

# AGE AND SEX DISTRIBUTION



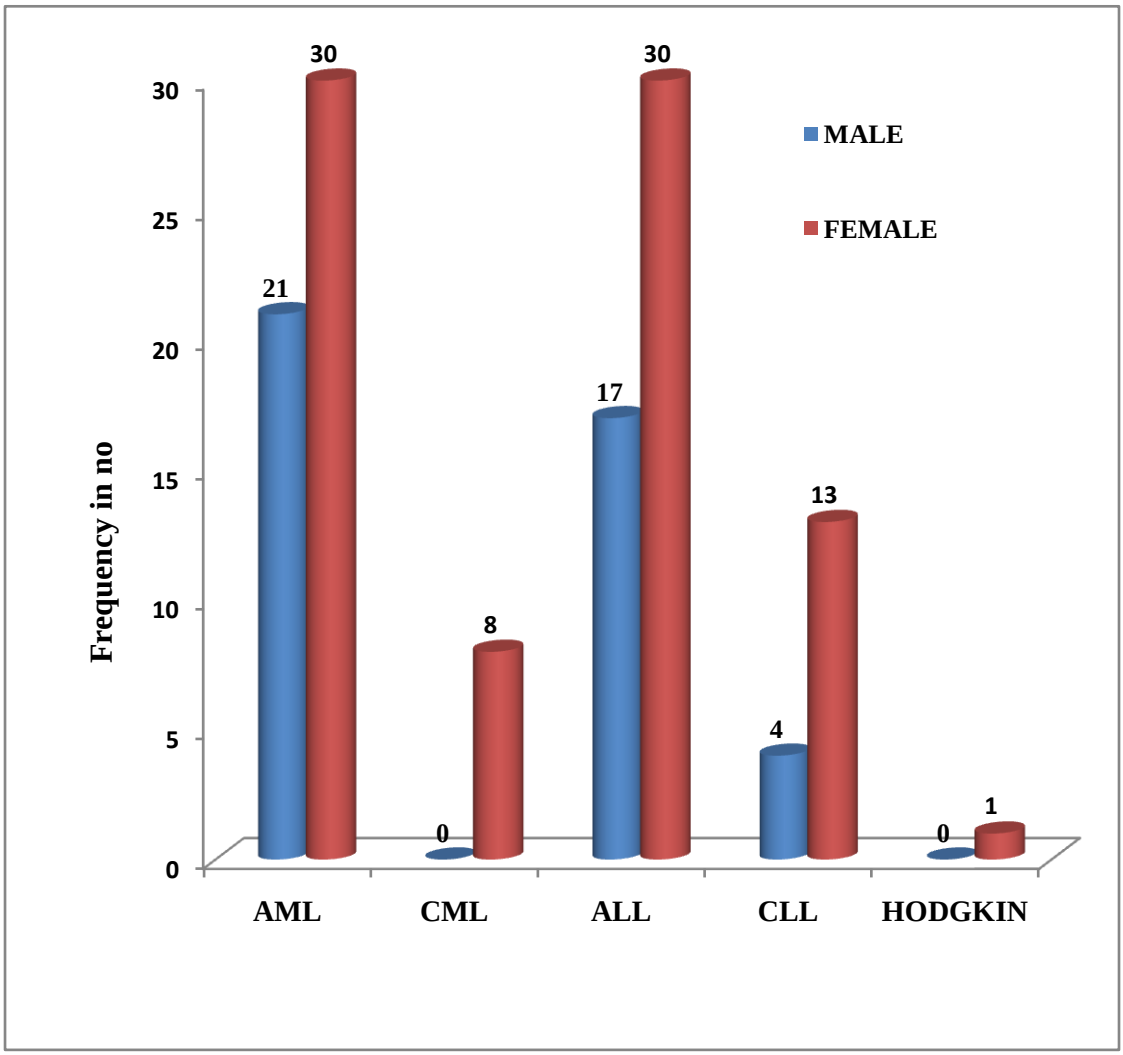
## HEMATOLOGICAL MALIGNANCIES

**TABLE 2:**

| DIAGNOSIS | MALE | FEMALE |
|---|---|---|
| **AML** | 21 | 30 |
| **CML** | 0 | 8 |
| **ALL** | 17 | 30 |
| **CLL** | 4 | 13 |
| **HODGKIN** | 0 | 1 |
| TOTAL | 42 | 82 |

This table shows the distribution of hematological malignancies in 124 patients, in which 51 patients had Acute myeloid leukemia (AML), 8 patients had Chronic myeloid leukemia (CML), 47 patients had Acute lymphoblastic leukemia (ALL), 17 patients had Chronic lymphoid leukemia (CLL) and one patient had Hodgkin lymphoma.

# HEMATOLOGICAL MALIGNANCIES



## CLINICAL FEATURES

**TABLE 3:**

**PRESENTING SYMPTOMS & SIGNS**

| SYMPTOMS & SIGNS | TOTAL | PERCENTAGE (N=124) |
|---|---|---|
| **SYMPTOMS** | | |
| **Cough** | 110 | 88.70 |
| **Expectoration** | 107 | 86.29 |
| **Breathlessness** | 66 | 53.22 |
| **Chest pain** | 18 | 14.51 |
| **Hemoptysis** | 20 | 16.12 |
| **Fever** | 90 | 72.58 |
| **SIGNS** | | |
| **Tachypnea** | 70 | 56.45 |
| **Wheeze** | 30 | 24.19 |
| **Crackles** | 38 | 30.64 |

This table shows that cough and expectoration were the common symptoms followed by fever.

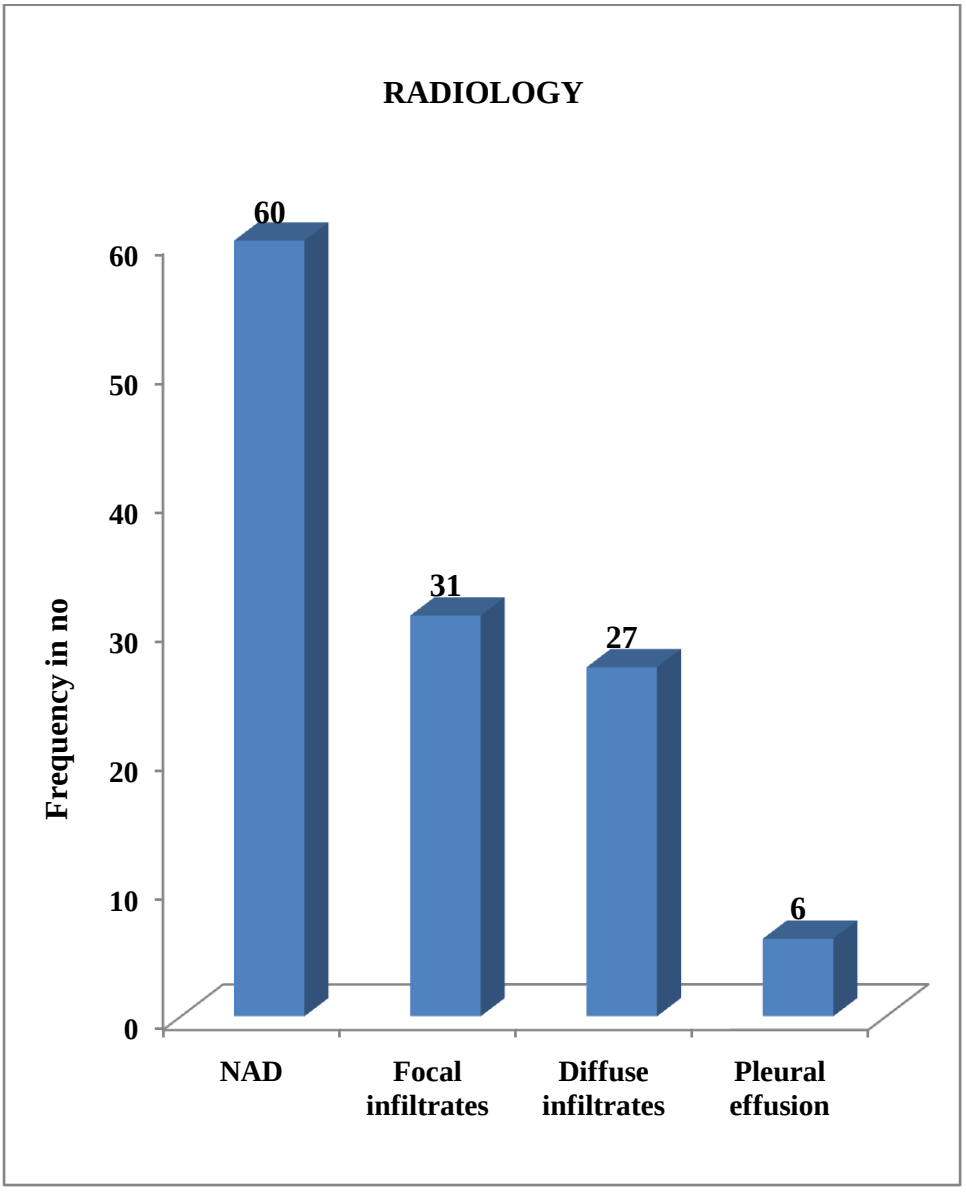
## RADIOLOGICAL FINDINGS

The radiological investigations were done in all 124 patients after obtaining informed written consent, findings observed in Radiography were 60 patients had no abnormal defect, 6 patients had pleural effusion, 58 patients had parenchymal infiltrates in them 31 had focal and 27 had diffuse infiltrate.

**TABLE 4:**

| RADIOLOGY | TOTAL | PERCENTAGE (N=124) |
|---|---|---|
| **NAD** | 60 | 48.38 |
| **Focal infiltrates** | 31 | 29.03 |
| **Diffuse infiltrates** | 27 | 17.74 |
| **Pleural effusion** | 6 | 4.83 |
| Total | 124 | 100 |

## RADIOLOGICAL FINDINGS



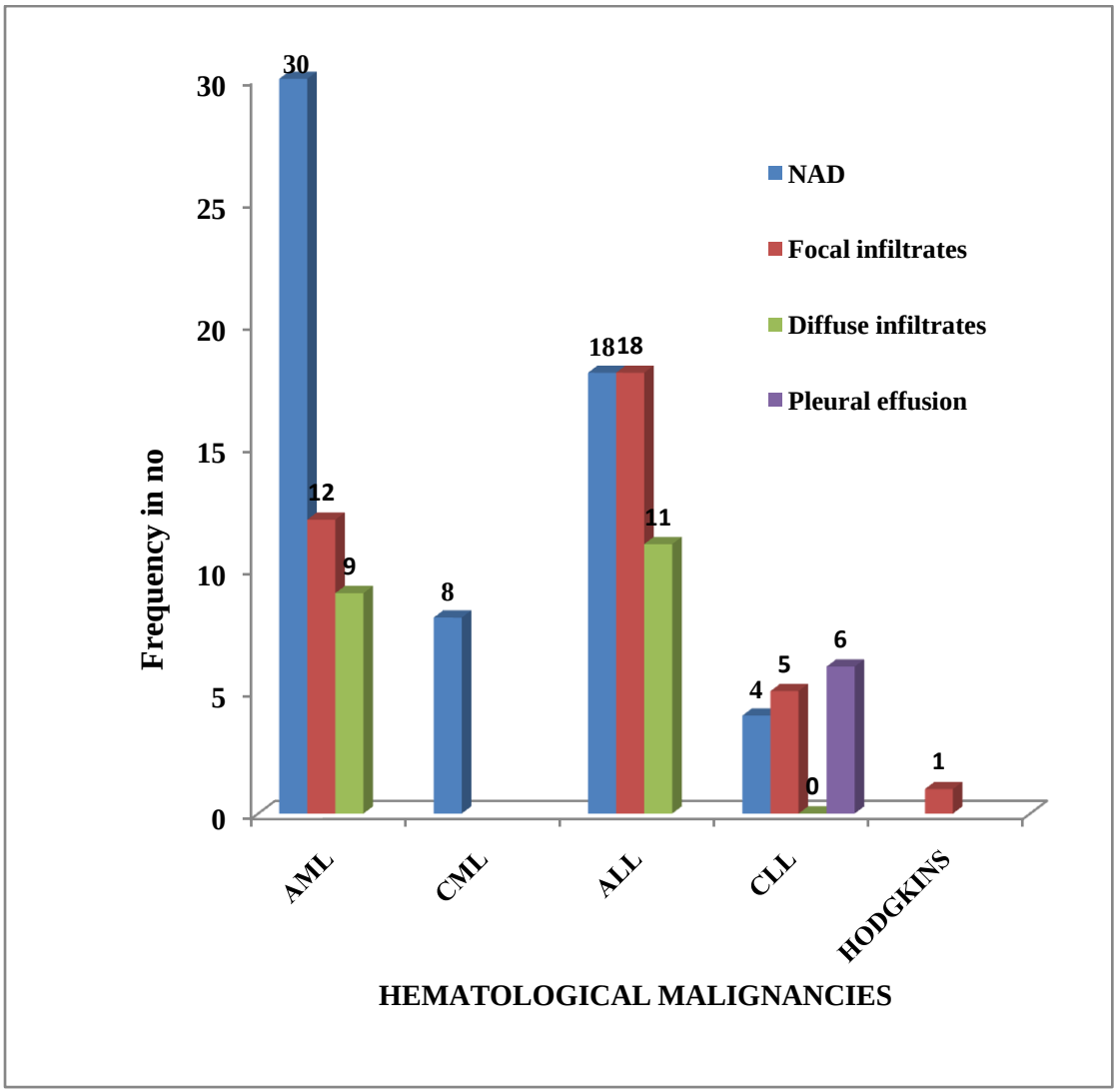
## RADIOLOGICAL FINDINGS IN HEMATOLOGICAL MALIGNANCIES

**TABLE 5:**

| Hematological Malignancies | RADIOLOGY | | | | Total |
|---|---|---|---|---|---|
| | NAD | Focal infiltrates | Diffuse infiltrates | Pleural effusion | |
| **AML** | 30 | 12 | 9 | - | 51 |
| **CML** | 8 | - | - | - | 8 |
| **ALL** | 18 | 18 | 11 | - | 47 |
| **CLL** | 4 | 5 | 2 | 6 | 17 |
| **HODGKINS** | - | 1 | - | - | 1 |
| Total | 60 | 36 | 22 | 6 | 124 |

This table shows the distribution of radiological findings in hematological malignancies, among 58 patients with parenchymal infiltrates, 50 patients were belonged to Acute leukemia (21 AML& 29 ALL) and 6 patients with pleural effusion were belonged to Chronic lymphoid leukemia (CLL).

## RADIOLOGICAL FINDINGS IN HEMATOLOGICAL MALIGNANCIES



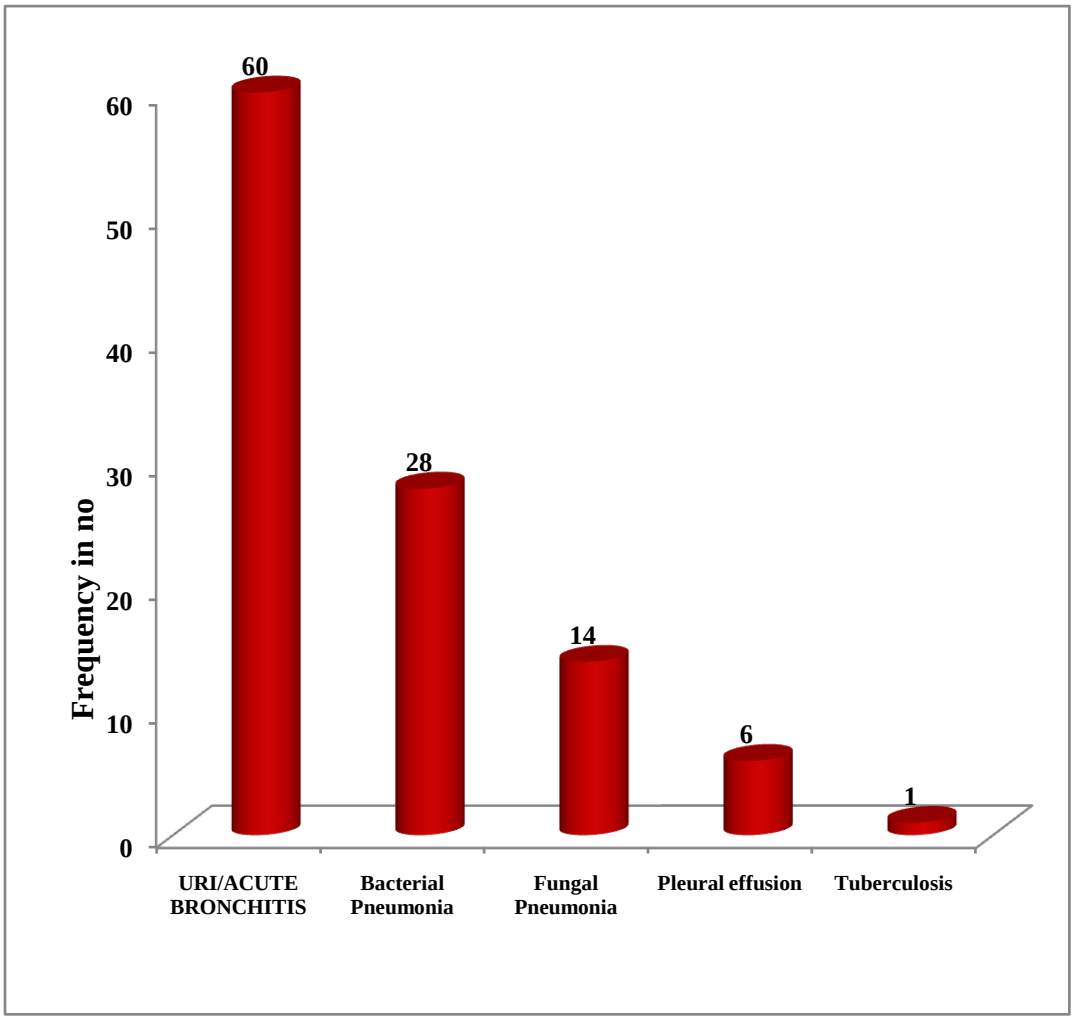
## RESPIRATORY DIAGNOSIS

**TABLE 6:**

| RESPIRATORY DIAGNOSIS | TOTAL | PERCENTAGE (N=124) |
|---|---|---|
| **URI/ACUTE BRONCHITIS** | 60 | 48.38 |
| **Bacterial Pneumonia** | 28 | 22.58 |
| **Fungal Pneumonia** | 14 | 11.29 |
| **Pleural effusion** | 6 | 4.83 |
| **Tuberculosis** | 1 | 0.80 |

This table shows that Upper respiratory tract /acute bronchitis is the common pulmonary abnormalities associated with hematological malignancies. 28 (22.58%) patients had bacterial pneumonia, 14 (11%) patients had fungal pneumonia, 6 (5%) patients had exudative pleural effusion and one patient was infected with Mycobacterium tuberculosis.

## RESPIRATORY DIAGNOSIS



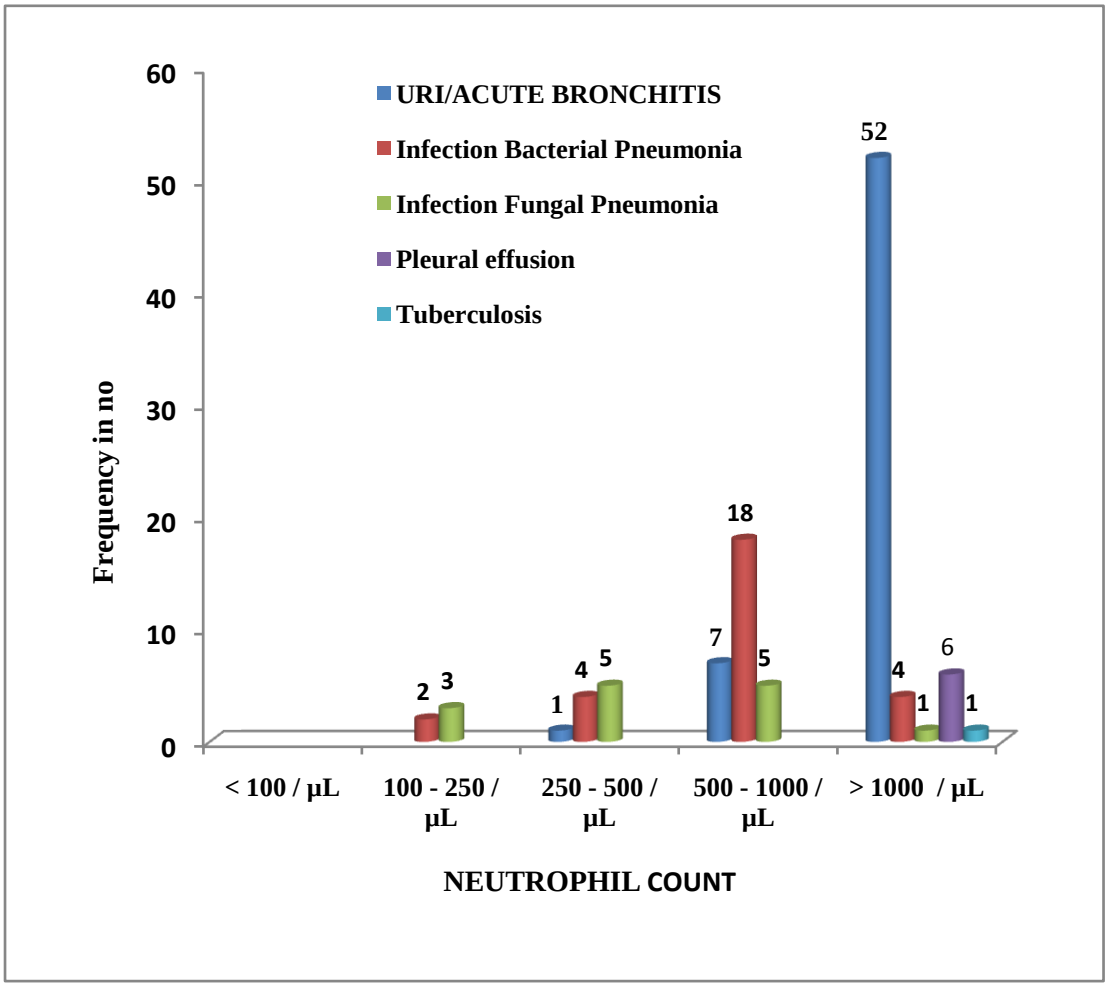
## NEUTROPHIL COUNT AND DIAGNOSIS

**TABLE 7:**

| NEUTROPHIL COUNT | CLINICAL DIAGNOSIS | | | | |
|---|---|---|---|---|---|
| | **URI/ACUTE BRONCHITIS** | **Infection Bacterial Pneumonia** | **Infection Fungal Pneumonia** | **Pleural effusion** | **Tuberculosis** |
| **< 100 / µL** | - | **-** | **-** | **-** | **-** |
| **100 - 250 / µL** | - | 2 | 3 | - | - |
| **250 - 500 / µL** | 1 | 4 | 5 | - | - |
| **500 - 1000 / µL** | 7 | 18 | 5 | - | - |
| **> 1000 / µL** | 52 | 4 | 1 | 6 | 1 |
| Total | 60 | 28 | 14 | 6 | 1 |

This table shows the distribution of infection in hematological malignancies in relation with neutrophil count. In patients with neutrophil count <1000/µl, there was a significant increase in occurrence of bacterial infection, and there was a significant increase in occurrence of fungal infection when the neutrophil count falls below 500/ µl.

# NEUTROPHIL COUNT AND DIAGNOSIS



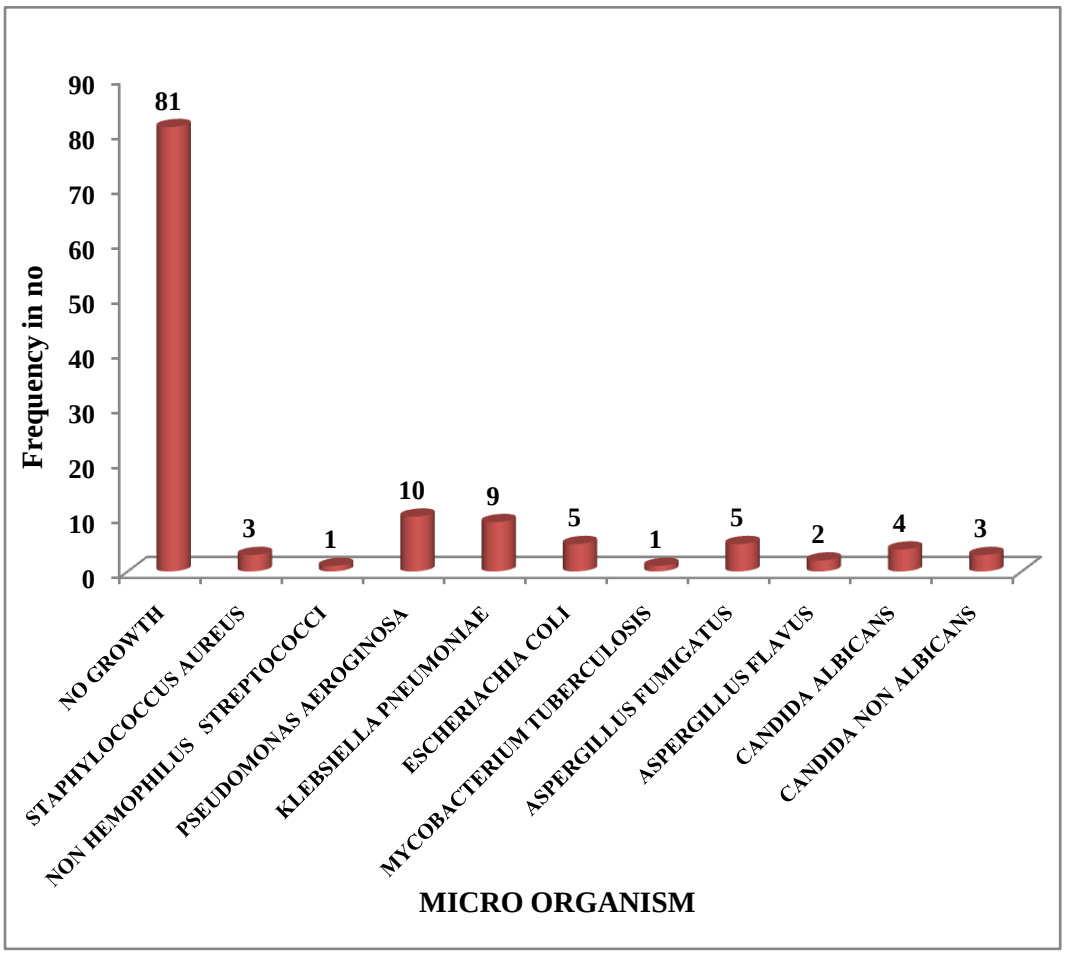
## MICROBIOLOGICAL SPECTRUM

**TABLE 8:**

| ORGANISM | TOTAL | PERCENTAGE (N=124) |
|---|---|---|
| NO GROWTH | 81 | 65.32 |
| BACTERIAL | 29 | |
| GRAM POSITIVE | 4 | |
| Staphylococcus aureus | 3 | 2.41 |
| non Hemophilus streptococci | 1 | 0.80 |
| GRAM NEGATIVE | 24 | |
| Pseudomonas aeroginosa | 10 | 8.06 |
| Klebsiella pneumoniae | 9 | 7.25 |
| Escherichia coli | 5 | 4.03 |
| Mycobacterium tuberculosis | 1 | 0.80 |
| FUNGAL | 14 | |
| Aspergillus fumigates | 5 | 4.03 |
| Aspergillus flavus | 2 | 1.61 |
| Candida albicans | 4 | 3.22 |
| Candida non albicans | 3 | 2.41 |

In this study, sputum cultures were done in all 124 patients. Findings observed were 81 patients had no growth in culture. 29 patients had bacterial growth among them Gram-negative organisms showed more predominance. 14 patients had fungal growth, with more predominance towards Aspergillus fumigates.

## MICROBIOLOGICAL SPECTRUM



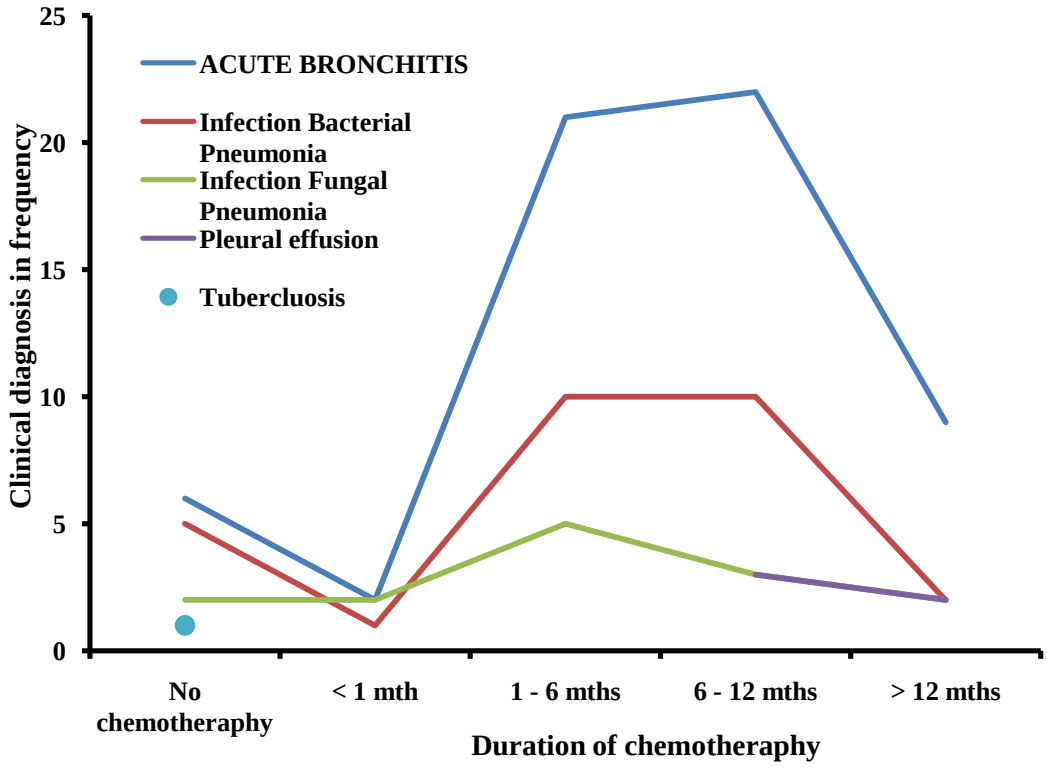
## RESPIRATORY DIAGNOSIS IN RELATION WITH DURATION OF CHEMOTHERAPY

### TABLE 9:

| Duration of chemotheraphy | CLINICAL DIAGNOSIS | | | | |
|---|---|---|---|---|---|
| | URI/ACUTE BRONCHITIS | Infection Bacterial Pneumonia | Infection Fungal Pneumonia | Pleural effusion | Tubercluosis |
| No chemotheraphy | 6 | 5 | 2 | 1 | 1 |
| < 1 mth | 2 | 1 | 2 | - | - |
| 1 - 6 mths | 21 | 10 | 5 | - | - |
| 6 - 12 mths | 22 | 10 | 3 | 3 | - |
| > 12 mths | 9 | 2 | 2 | 2 | - |
| Total | 60 | 28 | 14 | 6 | 1 |

This line diagram shows, more infections were seen after prolonged chemotherapy in patients with hematological malignancies.

**RESPIRATORY DIAGNOSIS IN RELATION WITH DURATION OF CHEMOTHERAPY**

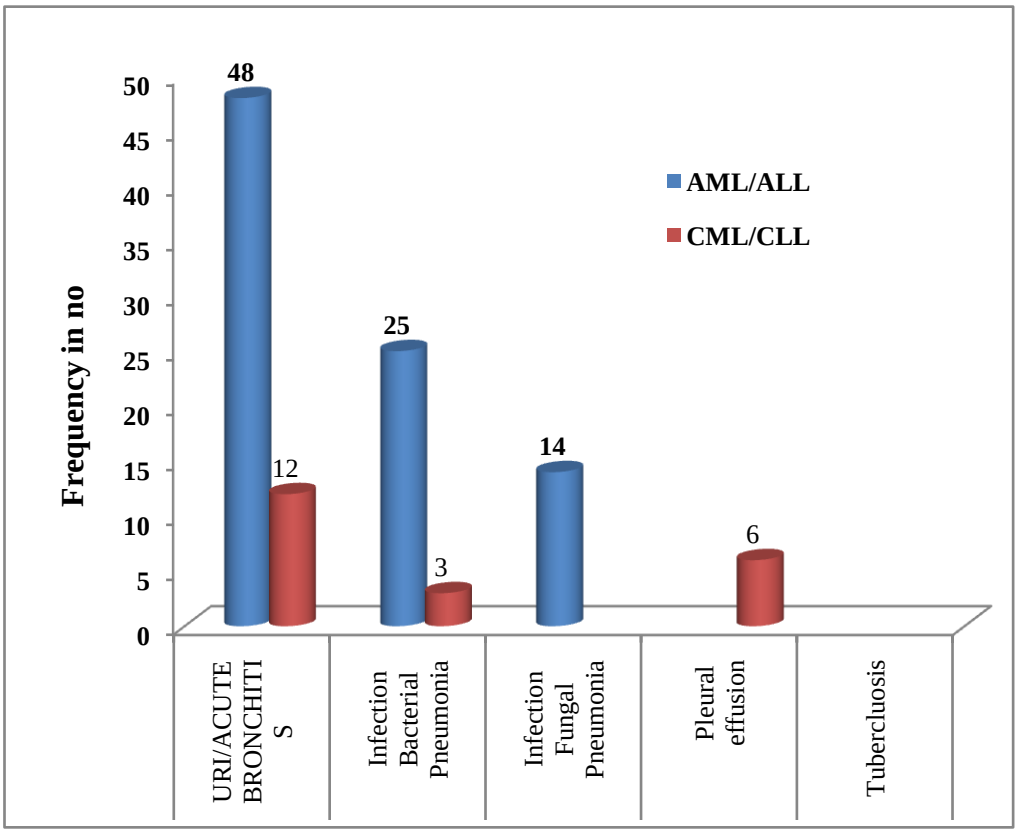


## RESPIRATORY DIAGNOSIS IN

## HEMATOLOGICAL MALIGNANCIES

### TABLE 10:

| Hematological Malignancies | CLINICAL DIAGNOSIS | | | | | Total |
|---|---|---|---|---|---|---|
| | URI/ACUTE BRONCHITIS | Infection Bacterial Pneumonia | Infection Fungal Pneumonia | Pleural effusion | Tuberculosis | |
| AML/ALL | 48 | 25 | 14 | | | 87 |
| CML/CLL | 12 | 3 | | 6 | | 21 |
| Total | 60 | 28 | 14 | 6 | 0 | 108 |



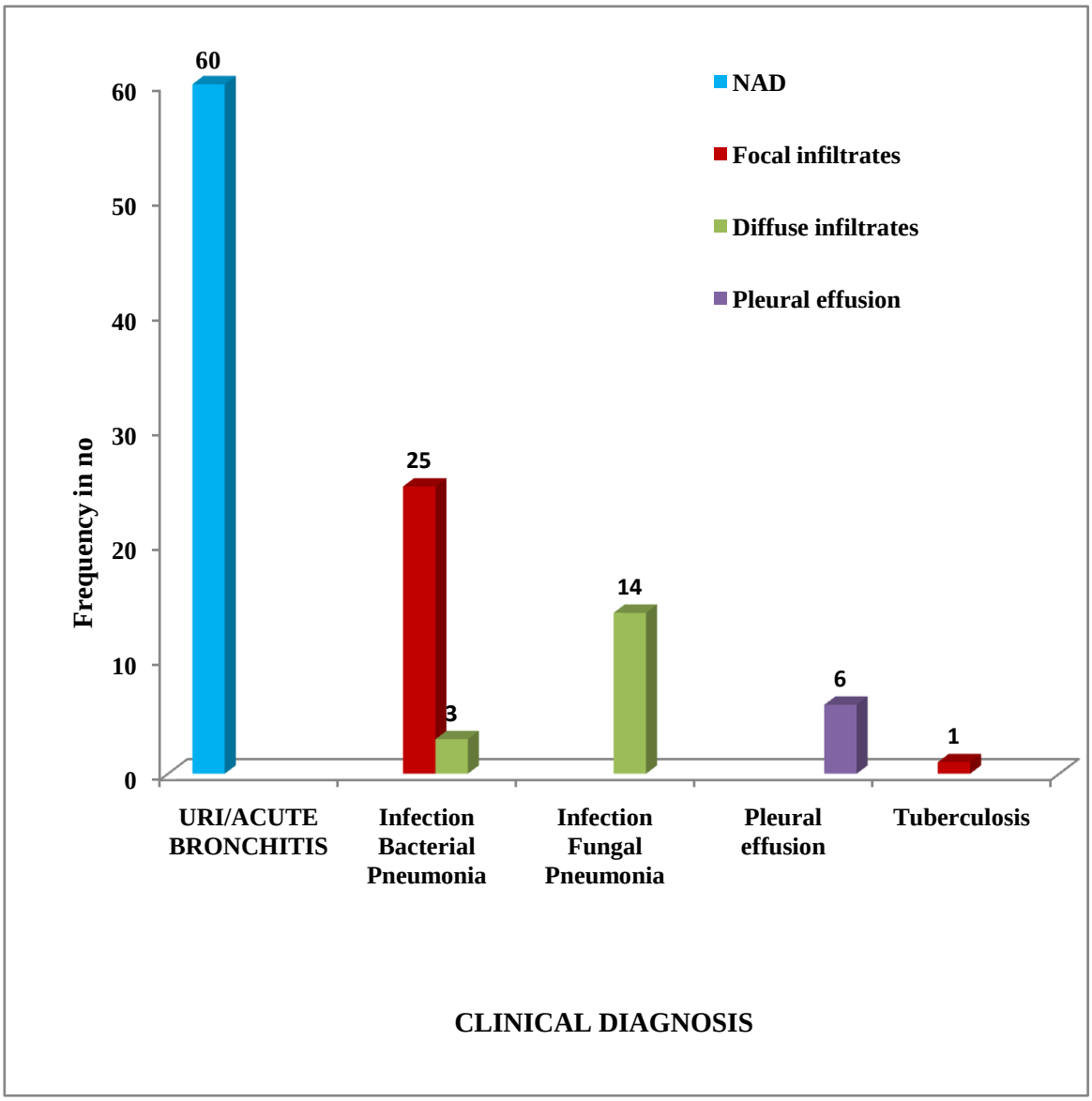
## RADIOLOGICAL FINDINGS & RESPIRATORY CONDITION

**TABLE 11:**

| CLINICAL DIAGNOSIS | RADIOLOGY | | | | Total |
|---|---|---|---|---|---|
| | NAD | Focal infiltrates | Diffuse infiltrates | Pleural effusion | |
| **URI/ACUTE BRONCHITIS** | 60 | - | - | - | 60 |
| **Infection Bacterial Pneumonia** | - | 25 | 3 | - | 28 |
| **Infection Fungal Pneumonia** | - | - | 14 | - | 14 |
| **Pleural effusion** | - | - | - | 6 | 6 |
| **Tuberculosis** | - | 1 | - | - | 1 |
| **Total** | 60 | 26 | 17 | 6 | 109 |

A cause for the disease process was established in 26 of 31 patients with focal infiltrates and 17 of 27 patients with diffuse infiltrates. The above table shows the causes. Of the 26 patients with focal infiltrate in which the cause could be established, 25 patients had bacterial infection and one patient had tuberculous infection. In contrast to the findings in the patients with focal infiltrate, 14 of 17 infections were caused by fungal organisms.

## RADIOLOGICAL FINDINGS & RESPIRATORY CONDITION



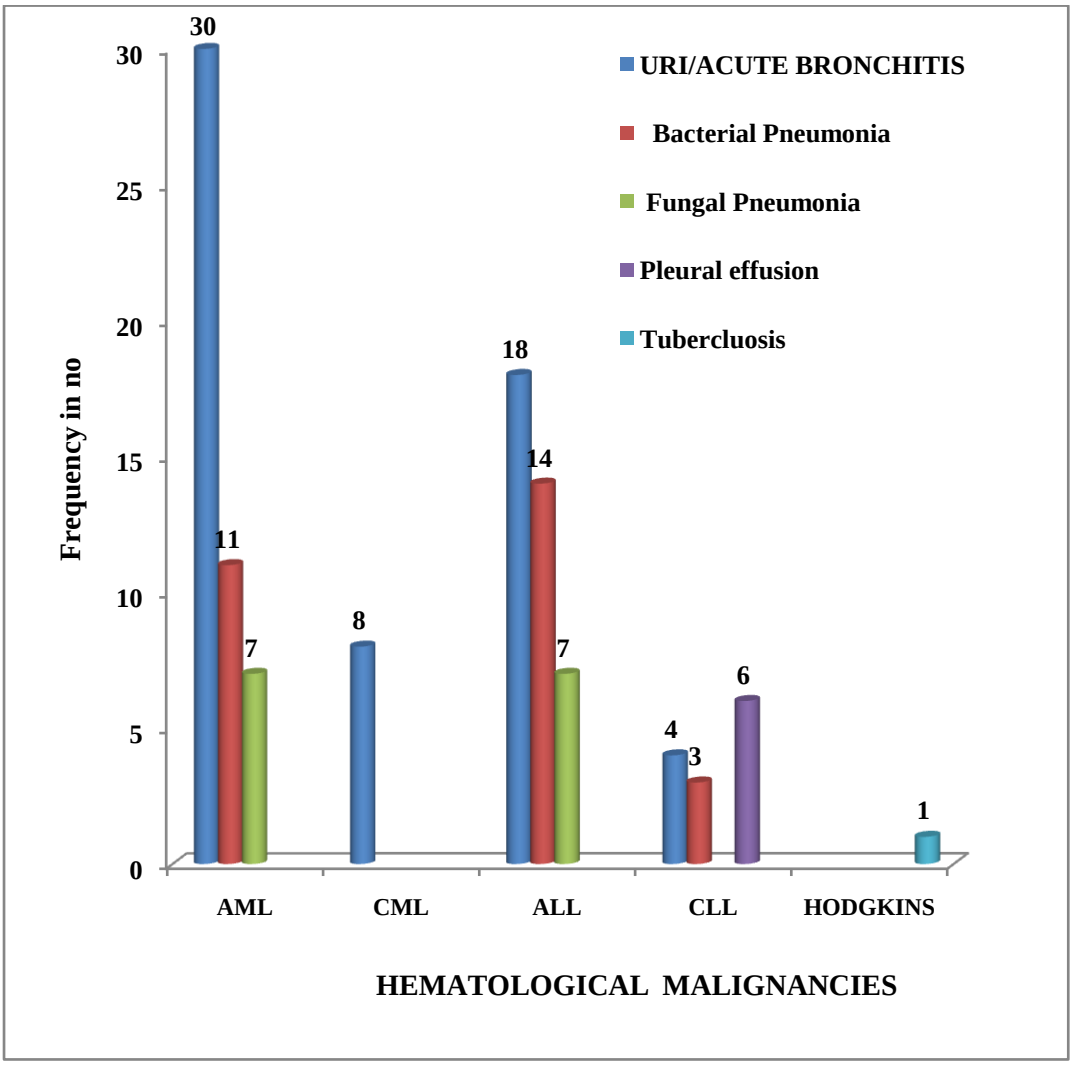
## RESPIRATORY DIAGNOSIS IN HEMATOLOGICAL MALIGNANCIES

**TABLE 12:**

| Hematological Malignancies | CLINICAL DIAGNOSIS | | | | |
|---|---|---|---|---|---|
| | URI/ACUTE BRONCHITIS | Infection Bacterial Pneumonia | Infection Fungal Pneumonia | Pleural effusion | Tuberculosis |
| **AML** | 30 | 11 | 7 | | |
| **CML** | 8 | | | | |
| **ALL** | 18 | 14 | 7 | | |
| **CLL** | 4 | 3 | | 6 | |
| **HODGKINS** | | | | | 1 |
| **Total** | 60 | 28 | 14 | 6 | 1 |

From this table we observed that out of 28 cases of bacterial pneumonias, 25 cases were occurred in acute leukemias and all cases of fungal pneumonias were occurred in acute leukemias. All 6 cases of exudative pleural effusion were occurred in chronic lymphocytic leukemia. Only one case of tuberculosis was noted, in Hodgkin lymphoma.

## RESPIRATORY DIAGNOSIS IN HEMATOLOGICAL MALIGNANCIES



# DISCUSSION

Hematological malignancies are a diverse group of disorders, in which various pulmonary manifestations are noted. Infections are common causes for increased morbidity and mortality in those patients with leukemia and lymphoma, among which lung is the commonest site (1).

Among hematological malignancies, incidences of infections are more common with Acute leukemia, that is Acute myeloid leukemia & Acute lymphoblastic leukemia.

A Rano et al in his study, says that infections by bacterial organisms mainly those caused by Pseudomonas aeroginosa and Staphylococcus aureus were the most frequent infections, followed by fungal organisms, mainly Aspergillus species were the second most common infectious cause of pulmonary infiltrates (4).

The degree of neutropenia either as a consequence of primary hematological malignancy or therapy is directly related to the incidence of serious bacterial and fungal pneumonias. There is a steady increase in the occurrence of infection with Absolute neutrophil count below 1000cells/µl.

Gerson and associates found Granulocytopenia to be the single most important predisposing factor for development of pulmonary infections in patients with leukemias and lymphomas. The incidence of infection in hematological neoplasms inversely proportional to the Absolute neutrophil count (16, 18).

Maj Michael F. Tenholder et al in his study about "pulmonary infiltrates in leukemia" says that, in 82% of patients presented with focal disease due to infection, the infection were primarily bacterial in origin in 86% of patients, with only 13% of patients with focal infiltrates were infected by opportunistic organisms. The episodes of diffuse pulmonary infiltrates occur during treatment were infectious only in 35% of patients. In contrast to the group with focal disease, 93% of patients were infected with opportunistic organisms.

In our study, 124 patients were included, among which 79% patients were belonged to Acute leukemia (Acute myeloid leukemia 41.12% & Acute lymphoblastic leukemia 37.90%).

The radiological findings observed in our study were, 60 patients had no abnormal defect, 6 patients had pleural effusion, and 58 patients had parenchymal infiltrates in them 31 had focal and 27 had diffuse

infiltrates. Among 58 patients with parenchymal infiltrates 50 (86%) patients were belonged to acute leukemias. Of the 31 patients with focal infiltrates the cause was established in 26 patients. Of the 26 patients with focal infiltrate in which the cause could be established, 25 patients had bacterial infection and one patient had tuberculous infection. Among 27 patients with diffuse infiltration etiology was identified in 17 patients, of whom 14 patients had fungal infection and in 3 patients bacterial pathogen had been isolated.

In patients with neutrophil count <1000/µl, there was a steady increase in incidence of bacterial infection, and there was a marked increase in incidence of fungal infection when the neutrophil count falls below 500/µl.

The sputum culture reports were positive more for bacterial organisms followed by fungal organisms. Among them Pseudomonas aeroginosa was the predominant organism, followed by Klebsiella pneumoniae and Aspergillus fumigates.

In our study, Upper respiratory tract infection and Acute bronchitis were the most common respiratory diagnosis, in patients with

hematological malignancies, followed by bacterial and fungal pneumonias. Tuberculosis was reported in only one patient.

Incidences of both bacterial and fungal were predominantly seen in Acute leukemias.

# CONCLUSION

1. Pulmonary infections are common cause for increased morbidity and mortality in patients with hematological malignancies.
2. Upper respiratory tract infection and acute bronchitis are the most common associated respiratory diagnosis in patients with hematological malignancies
3. Neutropenia is the major factor in determining the development of pulmonary infections.
4. Bacterial pneumonia predominantly present as focal infiltrates and fungal pneumonia as diffuse infiltrates.
5. Pulmonary infections are predominantly caused by gram-negative bacteria (Pseudomonas aeroginosa & Klebsiella pneumoniae) followed by fungal (Aspergillus fumigates) organisms.

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INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No: 04425305301
Fax : 04425363970

## CERTIFICATE OF APPROVAL

To
Dr.G. Ravikumar
PG in MD TB & Chest Diseases
Madras Medical College, Ch-3

Dear Dr.G. Ravikumar

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the proposal entitled " Evaluation of Pulmonary manifestations in hematological malignancies " No. 09022012.

The following members of Ethics Committee were present in the meeting held on 22.02.2012 conducted at Madras Medical College, Chennai -3.

| | | |
|---|---|---|
| 1. | Dr. S.K. Rajan, MD.FRCP.DSc | -- Chairperson |
| 2. | Prof. Pregna. B. Dolia MD<br>Vice Principal , Madras Medical College, Chennai -3 | -- Member Secretary |
| 3. | Prof. Md Ali. MD DM<br>Prof & HOD, Dept. of MGE, MMC, Chennai -3 | -- Member |
| 4. | Prof Vasanthi MD<br>Prof of Pharmacology, MMC, Ch-3 | -- Member |
| 5. | Prof. E. Dhandapani, MD<br>Prof of Internal Medicine, MMC, Ch-3 | -- Member |
| 6. | Thiru. S. Govindasamy . BA.BL | -- Lawyer |
| 7 . | Tmt. Arnold Soulina MA , MSW | -- Social Scientist |

We approve the proposal to be conducted in its presented form

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee

**INSTITUTE OF THORACIC MEDICINE**

**MMC & RGGGH, CHENNAI-3**

# "EVALUATION OF PULMONARY MANIFESTATIONS IN HEMATOLOGICAL MALIGNANCIES"

## PROFORMA

| | |
|---|---|
| NAME | |
| AGE | |
| SEX | |
| I.P NO. | |
| OCCUPATION | |

CLINICAL DATA:

- HEMATOLOGICAL MALIGNANCY TYPE
- TIME SINCE DIAGNOSIS
- TYPE TREATMENT FOR MALIGNANCY

1. NONE
2. ON CHEMOTHERAPY -DRUG AND DURATION
3. OFF CHEMOTHERAPY -DURATION
4. OTHER DRUGS
5. TRANSFUSION HISTORY

- RESPIRATORY SYMPTOMS

COUGH

EXPECTORATION

BREATHLESSNESS

HEMOPTYSIS

CHEST PAIN

FEVER

PAST HISTORY:

KNOWN CASE OF BRONCHIAL ASTHMA/ COPD

PRIOR TREATMENT FOR PULMONARY TUBERCULOSIS

DIABETES MELLITUS

PERSONAL HISTORY: SMOKER

ALCOHOL USE

CLINICAL EXAMINATION:

Conscious-

Oriented-

Dyspnea-

Respiratory rate-

Anemia-

Jaundice-

Pedal edema-

Cyanosis-

Clubbing-

VITAL SIGNS:

Pulse-

BP-

RR-

SYSTEMIC EXAMINATION:

CVS: S1S2-

Murmurs-

RS:

B/L Air entry-

NVBS-

Added Sounds-

P/A:

Organomegaly-

Free fluid-

INVESTIGATIONS:

Complete Blood Count:

| | |
|---|---|
| Total count | |
| Differential Count | |
| ESR | |
| Hemoglobin | |
| Packed Cell Volume | |
| Platelet Count | |

Renal Function Test:

| | |
|---|---|
| Blood Sugar | |
| Blood Urea | |
| Serum Creatinine | |
| Serum Sodium | |
| Serum Potassium | |

Liver Function Test:

| | |
|---|---|
| Total Bilirubin | |
| SGOT | |
| SGPT | |
| SAP | |
| Total Proteins | |
| Serum Albumin | |

ICTC:

SPO2:

SPUTUM FOR GRAM STAIN

NON TUBERCULOUS CULTURE

ACID FAST STAIN

FUNGAL SMEAR AND CULTURE

CYTOLOGY

BLOOD CULTURE (ENTERIC AND NON ENTERIC)

PLEURAL FLUID ANALYSIS:

SUGAR

PROTEIN

LDH

CELL COUNT

CYTOLOGY

AFB

GRAM STAIN

NON TUBERCULOUS CULTURE

CHEST X RAY:

CT/HRCT CHEST:

# INFORMATION SHEET

- Your specimen has been accepted.
- We are conducting a study on pulmonary manifestations in haematological malignancies patients attending Government
- General Hospital, Chennai and for that your specimen may be valuable to us.
- The purpose of this study is to diagnose certain pulmonary manifestations in haematological malignancies easily with the help of certain special tests.
- We are selecting certain cases and if your specimen is found eligible, we may be using your specimen to perform extra tests and special studies which in any way do not affect your final report or management.
- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.
- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.
- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator Signature of participant

Date :

# ஆராய்ச்சி தகவல்தாள்

சென்னை அரசு பொது மருத்துவமனைக்கு வரும் இரத்தப் புற்றுநோய் உள்ள நோயாளிகளிடம் நுரையீரலில் ஏற்படும் பாதிப்பை பற்றிய ஆராய்ச்சி இங்கு நடைபெற்று வருகின்றது.

இரத்தப் புற்றுநோய் பாதிக்கப்பட்ட நோயாளிகளுக்கு நுரையீரலில் பற்பல பாதிப்புகள் ஏற்பட வாய்ப்புகள் உள்ளது. அவற்றில் பொதுவாக ஏற்படும் பாதிப்பை அறியவும் அவற்றை எளிதில் கண்டறிவதற்கான வழிமுறைகளை ஆராயவும் இந்த ஆராய்ச்சி நடத்தப்படுகிறது.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களுடைய இரத்தம் மற்றும் சளியில் சில சிறப்பு பரிசோதனைகள் செய்து அதன் தகவல்களை ஆராய்வோம். தங்களுக்கு ஈ.சி.ஜி. நெஞ்சு நிழற்படம் மற்றும் நுரையீரலை சுற்றி நீர் சேர்ந்து இருந்தால் அந்த நீரை ஊசி மூலம் எடுத்து ஆராய்வோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பதால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்புக்கு உள்ளாகாது என்பதையும் தெரிவித்துக் கொள்கிறேன். முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையும் அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம். இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின் வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம். இந்த சிறப்பு பரிசோதனை முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிக்கப்படும் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

இடம் :

நாள் :

# PATIENT CONSENT FORM

**Title of the study: EVALUATION OF PULMONARY MANIFESTATIONS IN HEMATOLOGICAL MALIGNANCIES**

**Name of the Participant:**
_____.

**Name of the Principal (Co-Investigator): Dr.G.RAVI KUMAR**

**Name of the Institution:** Madras medical college and Rajiv Gandhi Government General
Hospital, Chennai-3

**Documentation of the informed consent**

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I , hereby give my consent to be included as a participant in "EVALUATION OF PULMONARY MANIFESTATIONS IN HEMATOLOGICAL MALIGNANCIES"

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the
   past _____ months including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.*****
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer
   unusual symptoms. *****
8. I have not participated in any research study within the past _____month(s). *****
9. I have not donated blood within the past _____ months—Add if the study involves extensive blood sampling. *****
10. I am aware of the fact that I can opt out of the study at any time without having to give any
    reason and this will not affect my future treatment in this hospital. *****
11. I am also aware that the investigator may terminate my participation in the study at any time,
    for any reason, without my consent. *****
12. I hereby give permission to the investigators to release the information obtained from me as

Result of participation in this study to the sponsors, regulatory authorities, Govt. agencies,
and IEC. I understand that they are publicly presented.

13. I have understand that my identity will be kept confidential if my data are publicly presented
14. I have had my questions answered to my satisfaction.
15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document

Name and signature / thumb impression of the participant (or legal representative if participant incompetents)

Name _____Signature_____
Date_____

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____
Date_____

## ஆராய்ச்சி ஒப்புதல் கடிதம்

## ஆராய்ச்சி தலைப்பு

இரத்தப் புற்றநோயால் பாதிக்கப்பட்டவர்களின் நுரையீரலில் ஏற்படும் நோய்களின் நிலை பற்றிய ஆய்வு.

பெயர் : தேதி :

வயது : உள் நோயாளி எண் :

பால் : ஆராய்ச்சி சேர்க்கை எண் :

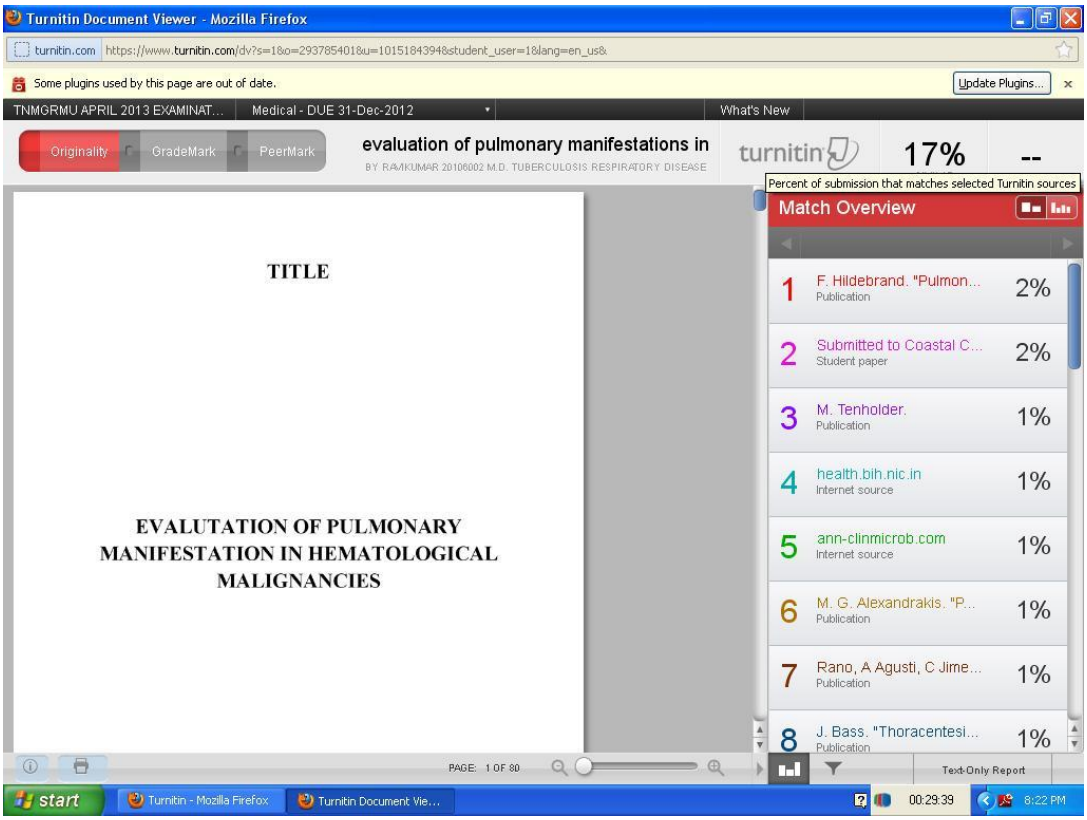
இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கமும் முழுமையாகவும், தெளிவாகவும் எனக்கு விளக்கப்பட்டது.

எனக்கு சளி, இரத்தப்பரிசோதனை, நெஞ்சு நிழற்படம், CT சேகன் மற்றும் தேவைப்பட்டால் நுரையீரலை சுற்றி நீர் சேர்ந்து இருந்தால் அதை எடுத்து பரிசோதனை செய்து கொள்ள சம்மதம்.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு எனது சம்மதத்தை தருகிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் நான் பங்கு பெறுகிறேன். மற்றும் நான் இந்த ஆராய்ச்சியில் இருந்து எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன். நான் என்னுடைய சுயநினைவுடன் மற்றும் முழு சுதந்திரத்துடன் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதிக்கிறேன்.

கையொப்பம்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**First 100 words of your submission**

TITLE EVALUTATION OF PULMONARY MANIFESTATION IN HEMATOLOGICAL MALIGNANCIES INTRODUCTION Leukemias and lymphomas are a diverse group of disorders. Myeloid neoplasms are heterogeneous group of disease which has an origin in a progenitor cell that normally gives rise to terminally differentiated cells of myeloid series (erythrocytes, granulocytes, monocytes and platelets). Three categories of myeloid neoplasia are recognized, they are: 1. Acute myelogenous leukemias, in which immature progenitor cells accumulate in the bone marrow 2. Myelodysplastic syndrome associated with ineffective hematopoiesis and leads to peripheral blood cytopenias 3. Chronic myeloproliferative disorders in which...